Recommended Concentrations and Doses of Mepivacaine Hydrochloride

Procedure	Concentration	Total Dose mL	Total Dose mg	Comments
Cervical, brachial, intercostal, pudendal nerve block	1%	5–40	50–400	Pudendal block: one half of total dose injected each side.
	2%	5–20	100–400	
Transvaginal block (paracervical plus pudendal)	1%	up to 30 (both sides)	up to 300 (both sides)	One half of total dose injected each side. See PRECAUTIONS.
Paracervical block	1%	up to 20 (both sides)	up to 200 (both sides)	One half of total dose injected each side. This is maximum recommended dose per 90-minute period in obstetrical and non-obstetrical patients. Inject slowly, 5 minutes between sides. See PRECAUTIONS.
Caudal and Epidural block	1%	15–30	150–300	*Use only single-dose vials which do not contain a preservative.
	1.5%	10–25	150–375	
	2%	10–20	200–400	
Infiltration	1%	up to 40	up to 400	An equivalent amount of a 0.5% solution (prepared by diluting the 1% solution with Sodium Chloride Injection, USP) may be used for large areas.
Therapeutic block (pain management)	1%	1–5	10–50	
	2%	1–5	20–100	

Unused portions of solutions not containing preservatives should be discarded.

*Dosage forms listed as POLOCAINE-MPF (Mepivacaine HCl Injection, USP) are single-dose solutions which do not contain a preservative.

their use. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine or epinephrine to enhance myocardial contractile force).

Endotracheal intubation, employing drugs and techniques familiar to the clinician may be indicated after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

Recent clinical data from patients experiencing local anesthetic induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis, plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted and maintained for a prolonged period if necessary. Recovery has been reported after prolonged resuscitative efforts.

The supine position is dangerous in pregnant women at term because of aortocaval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension, or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels should be accomplished.

The mean seizure dosage of mepivacaine in rhesus monkeys was found to be 18.8 mg/kg with mean arterial plasma concentration of 24.4 µg/mL. The intravenous and subcutaneous LD_{50} in mice is 23 mg/kg to 35 mg/kg and 280 mg/kg respectively.

DOSAGE AND ADMINISTRATION

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance and the physical condition of the patient. The smallest dose and concentration required to produce the desired result should be administered. Dosages of mepivacaine hydrochloride should be reduced for elderly and debilitated patients and patients with cardiac and/or liver disease. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional doses should be used when feasible.

For specific techniques and procedures, refer to standard textbooks.

The recommended single *adult* dose (or the total of a series of doses given in one procedure) of mepivacaine hydrochloride for unsedated, healthy, normal-sized individuals should not usually exceed 400 mg. The recommended dosage is based on requirements for the average adult and should be reduced for elderly or debilitated patients.

While maximum doses of 7 mg/kg (550 mg) have been administered without adverse effect, these are not recommended, except in exceptional circumstances and under no circumstances should the administration be repeated at intervals of less than 1½ hours. The total dose for any 24-hour period should not exceed 1,000 mg because of a slow accumulation of the anesthetic or its derivatives or slower than normal metabolic degradation or detoxification with repeat administration. (See CLINICAL PHARMACOLOGY and PRECAUTIONS.)

Pediatric patients tolerate the local anesthetic as well as adults. However, the pediatric dose should be ***carefully measured*** as a percentage of the total adult dose ***based on weight***, and should not exceed 5 mg/kg to 6 mg/kg (2.5 mg/lb to 3 mg/lb) in pediatric patients, especially those weighing less than 30 lbs. In pediatric patients ***under 3 years of age or weighing less than 30 lbs*** concentrations less than 2% (eg, 0.5% to 1.5%) should be employed.

Unused portions of solutions not containing preservatives, ie, those supplied in single-dose vials, should be discarded following initial use.

This product should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered.

[See table above]

HOW SUPPLIED

Single-dose vials and multiple-dose vials of POLOCAINE may be sterilized by autoclaving at 15 pound pressure, 121°C (250°F) for 15 minutes. Solutions of POLOCAINE may be renutoclaved when necessary. Do not administer solutions which are discolored or which contain particulate matter.

THESE SOLUTIONS ARE NOT INTENDED FOR SPINAL ANESTHESIA OR DENTAL USE.

POLOCAINE-MPF (Mepivacaine HCl Injection, USP) without preservatives is available as follows:

1% Single-dose vials of 30 mL (NDC 0186-0412-01)
1.5% Single-dose vials of 30 mL (NDC 0186-0418-01)
2% Single-dose vials of 20 mL (NDC 0186-0422-01)

POLOCAINE (Mepivacaine HCl Injection, USP) with preservatives is available as follows:

1% Multiple-dose vials of 50 mL (NDC 0186-0410-01)
2% Multiple-dose vials of 50 mL (NDC 0186-0420-01)

Store at controlled room temperature 15–30°C (59–86°F); brief exposure up to 40°C (104°F) does not adversely affect the product.

AstraZeneca LP, Wilmington, DE 19850
721668-03
Rev. 01/02

PRILOSEC®

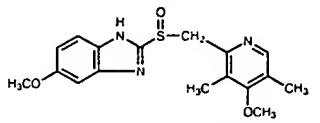
[prī-lō-sĕk]

(OMEPRAZOLE)

DELAYED-RELEASE CAPSULES

DESCRIPTION

The active ingredient in PRILOSEC (omeprazole) Delayed-Release Capsules is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

PRILOSEC is supplied as delayed-release capsules for oral administration. Each delayed-release capsule contains either 10 mg, 20 mg or 40 mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, mannitol, sodium lauryl sulfate and other ingredients. The capsule shells have the following inactive ingredients: gelatin-NF, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, synthetic black iron oxide, isopropanol, butyl alcohol, FD&C Blue #2, D&C Red #7 Calcium Lake, and, in addition, the 10 mg and 40 mg capsule shells also contain D&C Yellow #10.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism: Omeprazole

PRILOSEC Delayed-Release Capsules contain an enteric-coated granule formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma levels of omeprazole occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared to intravenous administration) is about 30–40% at doses of 20–40 mg, due in large part to presystemic metabolism. In healthy subjects the plasma half-life is 0.5 to 1 hour, and the total body clearance is 500–600 mL/min. Protein binding is approximately 95%. The bioavailability of omeprazole increases slightly upon repeated administration of PRILOSEC Delayed-Release Capsules.

Following single dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma — the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

In patients with chronic hepatic disease, the bioavailability increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared to the half-life in normals of 0.5–1 hour. Plasma clearance averaged 70 mL/min, compared to a value of 500–600 mL/min in normal subjects.

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 m^2, the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance. The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40 mg oral dose of omeprazole (buffered solution) was administered to healthy elderly volunteers, versus 58% in young volunteers given the same dose. Nearly 70% of the dose was recovered

Continued on next page

Prilosec—Cont.

in urine as metabolites of omeprazole and no unchanged drug was detected. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers.

In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians.

Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.

PRILOSEC Delayed-Release Capsule 40 mg was bioequivalent when administered with and without applesauce. However, PRILOSEC Delayed-Release Capsule 20 mg was not bioequivalent when administered with and without applesauce. When administered with applesauce, a mean 25% reduction in C_{max} was observed without a significant change in AUC for PRILOSEC Delayed-Release Capsule 20 mg. The clinical relevance of this finding is unknown.

The pharmacokinetics of omeprazole have been investigated in pediatric patients of different ages.

Pharmacokinetic Parameters of Omeprazole Following Single and Repeated Oral Administration in Pediatric Populations Compared to Adults

Single or Repeated Oral Dosing/ Parameter	Children† < 20 kg 2–5 years 10 mg	Children† > 20 kg 6–16 years 20 mg	Adults‡ (mean 76 kg) 23–29 years (n=12)
	Single Dosing		
C_{max}* (ng/mL)	288 (n=10)	495 (n=49)	668
AUC* (ng h/mL)	511 (n=7)	1140 (n=32)	1220
	Repeated Dosing		
C_{max}* (ng/mL)	539 (n=4)	851 (n=32)	1458
AUC* (ng h/mL)	1179 (n=2)	2276 (n=23)	3352

Note: * = plasma concentration adjusted to an oral dose of 1 mg/kg.
†Data from single and repeated dose studies
‡Data from a single and repeated dose study
Doses of 10, 20 and 40 mg Omeprazole as Enteric-Coated Granules

Following comparable mg/kg doses of omeprazole, younger children (2–5 years) have lower AUCs than children 6–16 years or adults; AUCs of the latter two groups did not differ, (see DOSAGE AND ADMINISTRATION, Pediatric Patients).

Pharmacokinetics: Combination Therapy with Antimicrobials

Omeprazole 40 mg daily was given in combination with clarithromycin 500 mg every 8 hours to healthy adult male subjects. The steady state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24}, and $T_{1/2}$ increases of 30%, 89% and 34% respectively) by the concomitant administration of clarithromycin. The observed increases in omeprazole plasma concentration were associated with the following pharmacological effects. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin.

The plasma levels of clarithromycin and 14-hydroxy-clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean C_{max} was 10% greater, the mean C_{min} was 27% greater, and the mean AUC_{0-8} was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14-hydroxy-clarithromycin, the mean C_{max} was 45% greater, the mean C_{min} was 57% greater, and the mean AUC_{0-8} was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

Clarithromycin Tissue Concentrations 2 hours after Dose[1]

Tissue	Clarithromycin	Clarithromycin + Omeprazole
Antrum	10.48 ± 2.01 (n = 5)	19.96 ± 4.71 (n = 5)
Fundus	20.81 ± 7.64 (n = 5)	24.25 ± 6.37 (n = 5)
Mucus	4.15 ± 7.74 (n = 4)	39.29 ± 32.79 (n = 4)

[1]Mean ± SD (μg/g)

For information on clarithromycin pharmacokinetics and microbiology, consult the clarithromycin package insert, CLINICAL PHARMACOLOGY section.

The pharmacokinetics of omeprazole, clarithromycin, and amoxicillin have not been adequately studied when all three drugs are administered concomitantly.

For information on amoxicillin pharmacokinetics and microbiology, see the amoxicillin package insert, ACTIONS, PHARMACOLOGY and MICROBIOLOGY sections.

Pharmacodynamics

Mechanism of Action

Omeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazules, that do not exhibit anticholinergic or H_2 histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Antisecretory Activity

After oral administration, the onset of the antisecretory effect of omeprazole occurs within one hour, with the maximum effect occurring within two hours. Inhibition of secretion is about 50% of maximum at 24 hours and the duration of inhibition lasts up to 72 hours. The antisecretory effect thus lasts far longer than would be expected from the very short (less than one hour) plasma half-life, apparently due to prolonged binding to the parietal H^+/K^+ ATPase enzyme. When the drug is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days.

Results from numerous studies of the antisecretory effect of multiple doses of 20 mg and 40 mg of omeprazole in normal volunteers and patients are shown below. The "max" value represents determinations at a time of maximum effect (2–6 hours after dosing), while "min" values are those 24 hours after the last dose of omeprazole.

Range of Mean Values from Multiple Studies of the Mean Antisecretory Effects of Omeprazole After Multiple Daily Dosing

Parameter	Omeprazole 20 mg Max	Omeprazole 20 mg Min	Omeprazole 40 mg Max	Omeprazole 40 mg Min
% Decrease in Basal Acid Output	78*	58–80	94*	80–93
% Decrease in Peak Acid Output	79*	50–59	88*	62–68
% Decrease in 24-hr. Intragastric Acidity		80–97		92–94

*Single Studies

Single daily oral doses of omeprazole ranging from a dose of 10 mg to 40 mg have produced 100% inhibition of 24-hour intragastric acidity in some patients.

Enterochromaffin-like (ECL) Cell Effects

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients (see CLINICAL PHARMACOLOGY, Pathological Hypersecretory Conditions). However, these studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

Serum Gastrin Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H_2-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3 to 3.6 fold vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Other Effects

Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single I.V. dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans. However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

The course of Barrett's esophagus in 106 patients was evaluated in a U.S. double-blind controlled study of PRILOSEC 40 mg b.i.d. for 12 months followed by 20 mg b.i.d. for 12 months or ranitidine 300 mg b.i.d. for 24 months. No clinically significant impact on Barrett's mucosa by antisecretory therapy was observed. Although neosquamous epithelium developed during antisecretory therapy, complete elimination of Barrett's mucosa was not achieved. No significant difference was observed between treatment groups in development of dysplasia in Barrett's mucosa and no patient developed esophageal carcinoma during treatment. No significant differences between treatment groups were observed in development of ECL cell hyperplasia, corpus atrophic gastritis, corpus intestinal metaplasia, or colon polyps exceeding 3 mm in diameter (see CLINICAL PHARMACOLOGY, Enterochromaffin-like (ECL) Cell Effects).

Clinical Studies

Duodenal Ulcer Disease

Active Duodenal Ulcer—In a multi-center, double-blind, placebo-controlled study of 147 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 2 and 4 weeks was significantly higher with PRILOSEC 20 mg once a day than with placebo ($p \leq 0.01$).

Treatment of Active Duodenal Ulcer
% of Patients Healed

	PRILOSEC 20 mg a.m. (n = 99)	Placebo a.m. (n = 48)
Week 2	*41	13
Week 4	*75	27

*($p \leq 0.01$)

Complete daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) in patients treated with PRILOSEC 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received PRILOSEC had complete relief of daytime pain ($p \leq 0.05$) and nighttime pain ($p \leq 0.01$).

In a multicenter, double-blind study of 293 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 4 weeks was significantly higher with PRILOSEC 20 mg once a day than with ranitidine 150 mg b.i.d. ($p < 0.01$).

Treatment of Active Duodenal Ulcer
% of Patients Healed

	PRILOSEC 20 mg a.m. (n = 145)	Ranitidine 150 mg b.i.d. (n = 148)
Week 2	42	34
Week 4	*82	63

*($p < 0.01$)

Healing occurred significantly faster in patients treated with PRILOSEC than in those treated with ranitidine 150 mg b.i.d. ($p < 0.01$).

In a foreign multinational randomized, double-blind study of 105 patients with endoscopically documented duodenal ulcer, 20 mg and 40 mg of PRILOSEC were compared to 150 mg b.i.d. of ranitidine at 2, 4 and 8 weeks. At 2 and 4 weeks both doses of PRILOSEC were statistically superior (per protocol) to ranitidine, but 40 mg was not superior to 20 mg of PRILOSEC, and at 8 weeks there was no significant difference between any of the active drugs.

Treatment of Active Duodenal Ulcer
% of Patients Healed

	PRILOSEC 20 mg (n = 34)	PRILOSEC 40 mg (n = 36)	Ranitidine 150 mg b.i.d. (n = 35)
Week 2	* 83	* 83	53
Week 4	* 97	*100	82
Week 8	100	100	94

*($p \leq 0.01$)

H. pylori Eradication in Patients with Duodenal Ulcer Disease Triple Therapy (PRILOSEC/clarithromycin/amoxicillin)—Three U.S., randomized, double-blind clinical studies in patients with *H. pylori* infection and duodenal ulcer disease (n = 558) compared PRILOSEC plus clarithromycin plus amoxicillin to clarithromycin plus amoxicillin. Two studies (126 and 127) were conducted in patients with an active duodenal ulcer, and the other study (M96-446) was conducted in patients with a history of a duodenal ulcer in the past 5 years but without an ulcer present at the time of enrollment. The dose regimen in the studies was PRILOSEC 20 mg b.i.d. plus clarithromycin 500 mg b.i.d. plus amoxicillin 1 g b.i.d. for 10 days; or clarithromycin 500 mg b.i.d. plus amoxicillin 1 g b.i.d. for 10 days. In studies 126 and 127, patients who took the omeprazole regimen also received an additional 18 days of PRILOSEC 20 mg q.d. Endpoints studied were eradication of *H. pylori* and duodenal ulcer healing (studies 126 and 127 only). *H. pylori* status was determined by CLOtest®, histology and culture in all three studies. For a given patient, *H. pylori* was considered eradicated if at least two of these tests were negative, and none was positive.

The combination of omeprazole plus clarithromycin plus amoxicillin was effective in eradicating *H. pylori*.

[See first table at top of next page]

Dual Therapy (PRILOSEC/clarithromycin)—Four randomized, double-blind, multi-center studies (M93-067, M93-100, M92-812b, and M93-058) evaluated PRILOSEC 40 mg q.d. plus clarithromycin 500 mg t.i.d. for 14 days, followed by

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PRILOSEC 20 mg q.d. (M93-067, M93-100, M93-058) or by PRILOSEC 40 mg q.d. (M92-812b) for an additional 14 days in patients with active duodenal ulcer associated with *H. pylori*. Studies M93-067 and M93-100 were conducted in the U.S. and Canada and enrolled 242 and 256 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 219 patients in Study M93-067 and 228 patients in Study M93-100. These studies compared the combination regimen to PRILOSEC and clarithromycin monotherapies. Studies M92-812b and M93-058 were conducted in Europe and enrolled 154 and 215 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 148 patients in study M92-812b and 208 patients in Study M93-058. These studies compared the combination regimen to omeprazole monotherapy. The results for the efficacy analyses for these studies are described below. *H. pylori* eradication was defined as no positive test (culture or histology) at 4 weeks following the end of treatment, and two negative tests were required to be considered eradicated of *H. pylori*. In the per-protocol analysis, the following patients were excluded: dropouts, patients with missing *H. pylori* tests post-treatment, and patients that were not assessed for *H. pylori* eradication because they were found to have an ulcer at the end of treatment.

The combination of omeprazole and clarithromycin was effective in eradicating *H. pylori*.

[See second table above]

Ulcer healing was not significantly different when clarithromycin was added to omeprazole therapy compared to omeprazole therapy alone.

The combination of omeprazole and clarithromycin was effective in eradicating *H. pylori* and reduced duodenal ulcer recurrence.

[See third table above]

Gastric Ulcer

In a U.S. multicenter, double-blind, study of omeprazole 40 mg once a day, 20 mg once a day, and placebo in 520 patients with endoscopically diagnosed gastric ulcer, the following results were obtained.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

	PRILOSEC 20 mg q.d. (n = 202)	PRILOSEC 40 mg q.d. (n = 214)	Placebo (n = 104)
Week 4	47.5**	55.6**	30.8
Week 8	74.8**	82.7**,*	48.1

**(p < 0.01) PRILOSEC 40 mg or 20 mg versus placebo
*(p < 0.05) PRILOSEC 40 mg versus 20 mg

For the stratified groups of patients with ulcer size less than or equal to 1 cm, no difference in healing rates between 40 mg and 20 mg was detected at either 4 or 8 weeks. For patients with ulcer size greater than 1 cm, 40 mg was significantly more effective than 20 mg at 8 weeks.

In a foreign, multinational, double-blind study of 602 patients with endoscopically diagnosed gastric ulcer, omeprazole 40 mg once a day, 20 mg once a day, and ranitidine 150 mg twice a day were evaluated.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

	PRILOSEC 20 mg q.d. (n = 200)	PRILOSEC 40 mg q.d. (n = 187)	Ranitidine 150 mg b.i.d. (n = 199)
Week 4	63.5	78.1**,**	56.3
Week 8	81.5	91.4**,**	78.4

**(p < 0.01) PRILOSEC 40 mg versus ranitidine
**(p < 0.01) PRILOSEC 40 mg versus 20 mg

Gastroesophageal Reflux Disease (GERD)
Symptomatic GERD

A placebo controlled study was conducted in Scandinavia to compare the efficacy of omeprazole 20 mg or 10 mg once daily for up to 4 weeks in the treatment of heartburn and other symptoms in GERD patients without erosive esophagitis. Results are shown below.

% Successful Symptomatic Outcome[a]

	PRILOSEC 20 mg a.m.	PRILOSEC 10 mg a.m.	Placebo a.m.
All patients	46*,† (n = 205)	31† (n = 199)	13 (n = 105)
Patients with confirmed GERD	56*,† (n = 115)	36† (n = 109)	14 (n = 59)

[a]Defined as complete resolution of heartburn
*(p < 0.005) versus 10 mg
†(p < 0.005) versus placebo

Erosive Esophagitis

In a U.S. multicenter double-blind placebo controlled study of 20 mg or 40 mg of PRILOSEC Delayed-Release Capsules in patients with symptoms of GERD and endoscopically diagnosed erosive esophagitis of grade 2 or above, the percentage healing rates (per protocol) were as follows:

Week	20 mg PRILOSEC (n = 83)	40 mg PRILOSEC (n = 87)	Placebo (n = 43)
4	39**	45**	7
8	74**	75**	14

**(p < 0.01) PRILOSEC versus placebo.

In this study, the 40 mg dose was not superior to the 20 mg dose of PRILOSEC in the percentage healing rate. Other controlled clinical trials have also shown that PRILOSEC is effective in severe GERD. In comparisons with histamine H_2-receptor antagonists in patients with erosive esophagitis, grade 2 or above, PRILOSEC in a dose of 20 mg was significantly more effective than the active controls. Complete daytime and nighttime heartburn relief occurred significantly faster (p < 0.01) in patients treated with PRILOSEC than in those taking placebo or histamine H_2-receptor antagonists.

In this and five other controlled GERD studies, significantly more patients taking 20 mg omeprazole (84%) reported complete relief of GERD symptoms than patients receiving placebo (12%).

Long Term Maintenance Treatment of Erosive Esophagitis

In a U.S. double-blind, randomized, multicenter, placebo controlled study, two dose regimens of PRILOSEC were studied in patients with endoscopically confirmed healed esophagitis. Results to determine maintenance of healing of erosive esophagitis are shown below.

Life Table Analysis

	PRILOSEC 20 mg q.d. (n = 138)	PRILOSEC 20 mg 3 days per week (n = 137)	Placebo (n = 131)
Percent in endoscopic remission at 6 months	*70	34	11

*(p < 0.01) PRILOSEC 20 mg q.d. versus PRILOSEC 20 mg 3 consecutive days per week or placebo.

Per-Protocol and Intent-to-Treat *H. pylori* Eradication Rates
% of Patients Cured [95% Confidence Interval]

	PRILOSEC +clarithromycin +amoxicillin		Clarithromycin +amoxicillin	
	Per-Protocol†	Intent-to-Treat‡	Per-Protocol†	Intent-to-Treat‡
Study 126	*77 [64, 86] (n = 64)	*69 [57, 79] (n = 80)	43 [31, 56] (n = 67)	37 [27, 48] (n = 84)
Study 127	*78 [67, 88] (n = 65)	*73 [61, 82] (n = 77)	41 [29, 54] (n = 68)	36 [26, 47] (n = 83)
Study M96-446	*90 [80, 96] (n = 69)	*83 [74, 91] (n = 84)	33 [24, 44] (n = 93)	32 [23, 42] (n = 99)

†Patients were included in the analysis if they had confirmed duodenal ulcer disease (active ulcer, studies 126 and 127; history of ulcer within 5 years, study M96-446) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology, and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy. The impact of eradication on ulcer recurrence has not been assessed in patients with a past history of ulcer.

‡Patients were included in the analysis if they had documented *H. pylori* infection at baseline and had confirmed duodenal ulcer disease. All dropouts were included as failures of therapy.

*(p < 0.05) versus clarithromycin plus amoxicillin.

H. pylori Eradication Rates (Per-Protocol Analysis at 4 to 6 Weeks)
% of Patients Cured [95% Confidence Interval]

	PRILOSEC + Clarithromycin	PRILOSEC	Clarithromycin
U.S. Studies			
Study M93-067	74 [60, 85]†‡ (n = 53)	0 [0, 7] (n = 54)	31 [18, 47] (n = 42)
Study M93-100	64 [51, 76]†‡ (n = 61)	0 [0, 6] (n = 59)	39 [24, 55] (n = 44)
Non U.S. Studies			
Study M92-812b	83 [71, 92]‡ (n = 60)	1 [0, 7] (n = 74)	N/A
Study M93-058	74 [64, 83]‡ (n = 86)	1 [0, 6] (n = 90)	N/A

†Statistically significantly higher than clarithromycin monotherapy (p < 0.05)
‡Statistically significantly higher than omeprazole monotherapy (p < 0.05)

Duodenal Ulcer Recurrence Rates by *H. pylori* Eradication Status
% of Patients with Ulcer Recurrence

	H. pylori eradicated[#]	*H. pylori* not eradicated[#]
U.S. Studies†		
6 months post-treatment		
Study M93-067	*35 (n = 49)	60 (n = 88)
Study M93-100	*8 (n = 53)	60 (n = 106)
Non U.S. Studies‡		
6 months post-treatment		
Study M92-812b	*5 (n = 43)	46 (n = 78)
Study M93-058	*6 (n = 53)	43 (n = 107)
12 months post-treatment		
Study M92-812b	*5 (n = 39)	68 (n = 71)

[#] *H. pylori* eradication status assessed at same timepoint as ulcer recurrence
†Combined results for PRILOSEC + clarithromycin, PRILOSEC, and clarithromycin treatment arms
‡Combined results for PRILOSEC + clarithromycin and PRILOSEC treatment arms
*(p ≤ 0.01) versus proportion with duodenal ulcer recurrence who were not *H. pylori* eradicated

In an international multicenter double-blind study, PRILOSEC 20 mg daily and 10 mg daily were compared to ranitidine 150 mg twice daily in patients with endoscopically confirmed healed esophagitis. The table below provides the results of this study for maintenance of healing of erosive esophagitis.

Life Table Analysis

	PRILOSEC 20 mg q.d. (n = 131)	PRILOSEC 10 mg q.d. (n = 133)	Ranitidine 150 mg b.i.d. (n = 128)
Percent in endoscopic remission at 12 months	*77	‡58	46

*(p = 0.01) PRILOSEC 20 mg q.d. versus PRILOSEC 10 mg q.d. or Ranitidine.
‡(p = 0.03) PRILOSEC 10 mg q.d. versus Ranitidine.

In patients who initially had grades 3 or 4 erosive esophagitis, for maintenance after healing 20 mg daily of PRILOSEC was effective, while 10 mg did not demonstrate effectiveness.

Pathological Hypersecretory Conditions

In open studies of 136 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, PRILOSEC Delayed-Release Capsules significantly inhibited gastric acid secretion and controlled associated symptoms of diar-

Continued on next page

Prilosec—Cont.

rhea, anorexia, and pain. Doses ranging from 20 mg every other day to 360 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric surgery, and below 5 mEq/hr in patients with prior gastric surgery. Initial doses were titrated to the individual patient need, and adjustments were necessary with time in some patients (see DOSAGE AND ADMINISTRATION). PRILOSEC was well tolerated at these high dose levels for prolonged periods (> 5 years in some patients). In most ZE patients, serum gastrin levels were not modified by PRILOSEC. However, in some patients serum gastrin increased to levels greater than those present prior to initiation of omeprazole therapy. At least 11 patients with ZE syndrome on long-term treatment with PRILOSEC developed gastric carcinoids. These findings are believed to be a manifestation of the underlying condition, which is known to be associated with such tumors, rather than the result of the administration of PRILOSEC (see ADVERSE REACTIONS).

Microbiology

Omeprazole and clarithromycin dual therapy and omeprazole, clarithromycin and amoxicillin triple therapy have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Helicobacter

Helicobacter pylori

Pretreatment Resistance

Clarithromycin pretreatment resistance rates were 3.5% (4/113) in the omeprazole/clarithromycin dual therapy studies (M93-067, M93-100) and 9.3% (41/439) in omeprazole/clarithromycin/amoxicillin triple therapy studies (126, 127, M96-446).

Amoxicillin pretreatment susceptible isolates (≤ 0.25 µg/mL) were found in 99.3% (436/439) of the patients in the omeprazole/clarithromycin/amoxicillin triple therapy studies (126, 127, M96-446). Amoxicillin pretreatment minimum inhibitory concentrations (MICs) > 0.25 µg/mL occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin and amoxicillin study arm. One patient had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 µg/mL by Etest®.

[See table below]

Patients not eradicated of *H. pylori* following omeprazole/clarithromycin/amoxicillin triple therapy or omeprazole/clarithromycin dual therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, if possible. Patients with clarithromycin resistant *H. pylori* should not be treated with any of the following: omeprazole/clarithromycin dual therapy, omeprazole/clarithromycin/amoxicillin triple therapy, or other regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the triple therapy clinical trials, 84.9% (157/185) of the patients in the omeprazole/clarithromycin/amoxicillin treatment group who had pretreatment amoxicillin susceptible MICs (≤ 0.25 µg/mL) were eradicated of *H. pylori* and 15.1% (28/185) failed therapy. Of the 28 patients who failed triple therapy, 11 had no post-treatment susceptibility test results and 17 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Eleven of the patients who failed triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs.

Susceptibility Test for *Helicobacter pylori*

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs[1]. One to three microliters of an inoculum equivalent to a No. 2 McFarland standard ($1 \times 10^7 - 1 \times 10^8$ CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

Clarithromycin MIC (µg/mL)[a]	Interpretation	
≤ 0.25	Susceptible	(S)
0.5	Intermediate	(I)
≥ 1.0	Resistant	(R)
Amoxicillin MIC (µg/mL)[a,b]	**Interpretation**	
≤ 0.25	Susceptible	(S)

[a] These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.

[b] There were not enough organisms with MICs > 0.25 µg/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

Microorganism	Antimicrobial Agent	MIC (µg/mL)[a]
H. pylori ATCC 43504	Clarithromycin	0.016–0.12 (µg/mL)
H. pylori ATCC 43504	Amoxicillin	0.016–0.12 (µg/mL)

[a] These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

INDICATIONS AND USAGE

Duodenal Ulcer

PRILOSEC Delayed-Release Capsules are indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

PRILOSEC Delayed-Release Capsules, in combination with clarithromycin and amoxicillin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or up to 1-year history) to eradicate *H. pylori*.

PRILOSEC Delayed-Release Capsules, in combination with clarithromycin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori*.

Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence (see CLINICAL PHARMACOLOGY, Clinical Studies and DOSAGE AND ADMINISTRATION).

Among patients who fail therapy, PRILOSEC with clarithromycin is more likely to be associated with the development of clarithromycin resistance as compared with triple therapy. In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See Microbiology section, and the clarithromycin package insert, MICROBIOLOGY section.)

Gastric Ulcer

PRILOSEC Delayed-Release Capsules are indicated for short-term treatment (4–8 weeks) of active benign gastric ulcer (see CLINICAL PHARMACOLOGY, Clinical Studies, Gastric Ulcer).

Treatment of Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

PRILOSEC Delayed-Release Capsules are indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis

PRILOSEC Delayed-Release Capsules are indicated for the short-term treatment (4–8 weeks) of erosive esophagitis which has been diagnosed by endoscopy (see CLINICAL PHARMACOLOGY, Clinical Studies).

The efficacy of PRILOSEC used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (eg, heartburn), additional 4–8 week courses of omeprazole may be considered.

Maintenance of Healing of Erosive Esophagitis

PRILOSEC Delayed-Release Capsules are indicated to maintain healing of erosive esophagitis.

Controlled studies do not extend beyond 12 months.

Pathological Hypersecretory Conditions

PRILOSEC Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

CONTRAINDICATIONS

Omeprazole

PRILOSEC Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation.

Clarithromycin

Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic.

Concomitant administration of clarithromycin with cisapride, pimozide, or terfenadine is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozide, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of hepatic metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported. (Please refer to full prescribing information for clarithromycin before prescribing.)

Amoxicillin

Amoxicillin is contraindicated in patients with a history of allergic reaction to any of the penicillins. (Please refer to full prescribing information for amoxicillin before prescribing.)

WARNINGS

Clarithromycin

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (See WARNINGS in prescribing information for clarithromycin.)

Amoxicillin

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. BEFORE INITIATING THERAPY WITH AMOXICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. (See WARNINGS in prescribing information for amoxicillin.)

Antimicrobials

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. (See WARNINGS in prescribing information for clarithromycin and amoxicillin.)

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General

Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes[a]

Clarithromycin Pretreatment Results		Clarithromycin Post-treatment Results				
		H. pylori negative - eradicated	*H. pylori* positive - not eradicated Post-treatment susceptibility results			
			S[b]	I[b]	R[b]	No MIC
Dual Therapy - (omeprazole 40 mg q.d./clarithromycin 500 mg t.i.d. for 14 days followed by omeprazole 20 mg q.d. for another 14 days) (Studies M93-067, M93-100)						
Susceptible[b]	108	72	1		26	9
Intermediate[b]	1				1	
Resistant[b]	4				4	
Triple Therapy - (omeprazole 20 mg b.i.d./clarithromycin 500 mg b.i.d./amoxicillin 1 g b.i.d. for 10 days - Studies 126, 127, M96-446; followed by omeprazole 20 mg q.d. for another 18 days - Studies 126, 127)						
Susceptible[b]	171	153	7		3	8
Intermediate[b]						
Resistant[b]	14	4	1		6	3

[a] Includes only patients with pretreatment clarithromycin susceptibility test results

[b] Susceptible (S) MIC ≤ 0.25 µg/mL, Intermediate (I) MIC 0.5 – 1.0 µg/mL, Resistant (R) MIC ≥ 2 µg/mL

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

Information for Patients

PRILOSEC Delayed-Release Capsules should be taken before eating. Patients should be cautioned that the PRILOSEC Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole.

For patients who have difficulty swallowing capsules, the contents of a PRILOSEC Delayed-Release Capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

Drug Interactions

Other

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (eg, cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with PRILOSEC.

Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (eg, ketoconazole, ampicillin esters, and iron salts). In the clinical trials, antacids were used concomitantly with the administration of PRILOSEC.

Combination Therapy with Clarithromycin

Co-administration of omeprazole and clarithromycin have resulted in increases in plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin (see also CLINICAL PHARMACOLOGY, Pharmacokinetics: Combination Therapy with Antimicrobials).

Concomitant administration of clarithromycin with cisapride, pimozide, or terfenadine is contraindicated.

There have been reports of an interaction between erythromycin and astemizole resulting in QT prolongation and torsades de pointes. Concomitant administration of erythromycin and astemizole is contraindicated. Because clarithromycin is also metabolized by cytochrome P450, concomitant administration of clarithromycin with astemizole is not recommended. (see also CONTRAINDICATIONS, Clarithromycin, above. Please refer to full prescribing information for clarithromycin before prescribing).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 4 to 352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 35 times the human dose) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. An unusual primary malignant tumor in the stomach was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53+/- transgenic mouse carcinogenicity study was not positive.

Omeprazole was not mutagenic in an *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell assay and an *in vivo* rat liver DNA damage assay. A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an *in vivo* bone marrow chromosome aberration test. A second mouse micronucleus study at 2000 times the human dose, but with different (suboptimal) sampling times, was negative.

In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals.

Pregnancy

Omeprazole

Pregnancy Category C

Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clarithromycin

Pregnancy Category C. See WARNINGS (above) and full prescribing information for clarithromycin before using in pregnant women.

Nursing Mothers

It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased weight gain in pups. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of PRILOSEC have been established in the age group 2 years to 16 years for the treatment of acid-related gastrointestinal diseases, including the treatment of symptomatic GERD, treatment of erosive esophagitis, and the maintenance of healing of erosive esophagitis. The safety and effectiveness of PRILOSEC have not been established for pediatric patients less than 2 years of age. Use of PRILOSEC in the age group 2 years to 16 years is supported by evidence from adequate and well-controlled studies of PRILOSEC in adults with additional clinical, pharmacokinetic, and safety studies performed in pediatric patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism: Omeprazole).

Treatment of Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

In an uncontrolled, open-label study of patients aged 2 years to 16 years with a history of symptoms suggestive of nonerosive GERD, 113 patients were assigned to receive a single daily dose of omeprazole (10 mg or 20 mg, based on body weight) either as an intact capsule or as an open capsule in applesauce. Results showed success rates of 60% (10 mg omeprazole) and 59% (20 mg omeprazole) in reducing the number and intensity of either pain-related symptoms or vomiting/regurgitation episodes.

Erosive Esophagitis

In an uncontrolled, open-label dose-titration study, healing of erosive esophagitis in pediatric patients aged 1 to 16 years required doses that ranged from 0.7 to 3.5 mg/kg/day (80 mg/day). Doses were initiated at 0.7 mg/kg/day. Doses were increased in increments of 0.7 mg/kg/day (if intra-esophageal pH showed a pH of < 4 for less than 6% of a 24-hour study). After titration, patients remained on treatment for 3 months. Forty-four percent of the patients were healed on a dose of 0.7 mg/kg body weight; most of the remaining patients were healed with 1.4 mg/kg after an additional 3 months' treatment. Erosive esophagitis was healed in 51 of 57 (90%) children who completed the first course of treatment in the healing phase of the study. In addition, after 3 months of treatment, 33% of the children had no overall symptoms, 57% had mild reflux symptoms, and 40% had less frequent regurgitation/vomiting.

Maintenance of Healing of Erosive Esophagitis

In an uncontrolled, open-label study of maintenance of healing of erosive esophagitis in 46 pediatric patients, 54% of patients required half the healing dose. The remaining patients increased the healing dose (0.7 to a maximum of 2.8 mg/kg/day) either for the entire maintenance period, or returned to half the dose before completion. Of the 46 patients who entered the maintenance phase, 19 (41%) had no relapse. In addition, maintenance therapy in erosive esophagitis patients resulted in 63% of patients having no overall symptoms.

Safety

The safety of PRILOSEC Delayed-Release Capsules has been assessed in 310 pediatric patients aged 0 to 16 years and 62 physiologically normal volunteers aged 2 years to 16 years. Of the 310 pediatric patients with acid-related disease, a group of 46 who had documented healing of erosive esophagitis after 3 months of treatment continued on maintenance therapy for up to 749 days.

PRILOSEC Delayed-Release Capsules administered to pediatric patients was generally well tolerated with an adverse event profile resembling that in adults. Unique to the pediatric population, however, adverse events of the respiratory system were most frequently reported in both the 0 to 2 year and 2 to 16 year age groups (46.2% and 18.5%, respectively). Similarly, otitis media was frequently reported in the 0 to 2 year age group (22.6%), and accidental injuries were reported frequently in the 2 to 16 year age group (3.8%).

Geriatric Use

Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the US and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

PRILOSEC Delayed-Release Capsules were generally well tolerated during domestic and international clinical trials in 3096 patients.

In the U.S. clinical trial population of 465 patients (including duodenal ulcer, Zollinger-Ellison syndrome and resistant ulcer patients), the following adverse experiences were reported to occur in 1% or more of patients on therapy with PRILOSEC. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug:

	Omeprazole (n = 465)	Placebo (n = 64)	Ranitidine (n = 195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

The following adverse reactions which occurred in 1% or more of omeprazole-treated patients have been reported in international double-blind, and open-label, clinical trials in which 2,631 patients and subjects received omeprazole.

Incidence of Adverse Experiences ≥ 1%
Causal Relationship not Assessed

	Omeprazole (n = 2631)	Placebo (n = 120)
Body as a Whole, site unspecified		
Abdominal pain	5.2	3.3
Asthenia	1.3	0.8
Digestive System		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid regurgitation	1.9	3.3
Nervous System / Psychiatric		
Headache	2.9	2.5

Additional adverse experiences occurring in < 1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to PRILOSEC was unclear.

Body as a Whole: Allergic reactions, including, rarely, anaphylaxis (see also *Skin* below), fever, pain, fatigue, malaise, abdominal swelling

Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.

Gastro-duodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with PRILOSEC. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic: Mild and, rarely, marked elevations of liver function tests (ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)). In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic / Nutritional: Hyponatremia, hypoglycemia, weight gain

Musculoskeletal: Muscle cramps, myalgia, muscle weakness, joint pain, leg pain

Nervous System / Psychiatric: Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia

Continued on next page

Prilosec—Cont.

Respiratory: Epistaxis, pharyngeal pain
Skin: Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, alopecia, dry skin, hyperhidrosis
Special Senses: Tinnitus, taste perversion
Urogenital: Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia
Hematologic: Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.
The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

Combination Therapy for *H. pylori* Eradication

In clinical trials using either dual therapy with PRILOSEC and clarithromycin, or triple therapy with PRILOSEC, clarithromycin, and amoxicillin, no adverse experiences peculiar to these drug combinations have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with omeprazole, clarithromycin, or amoxicillin.
Triple Therapy (PRILOSEC/clarithromycin/amoxicillin) — The most frequent adverse experiences observed in clinical trials using combination therapy with PRILOSEC, clarithromycin, and amoxicillin (n = 274) were diarrhea (14%), taste perversion (10%), and headache (7%). None of these occurred at a higher frequency than that reported by patients taking the antimicrobial drugs alone.
For more information on clarithromycin or amoxicillin, refer to the respective package inserts, ADVERSE REACTIONS sections.
Dual Therapy (PRILOSEC/clarithromycin) — Adverse experiences observed in controlled clinical trials using combination therapy with PRILOSEC and clarithromycin (n = 346) which differed from those previously described for omeprazole alone were: Taste perversion (15%), tongue discoloration (2%), rhinitis (2%), pharyngitis (1%) and flu syndrome (1%).
For more information on clarithromycin, refer to the clarithromycin package insert, ADVERSE REACTIONS section.

OVERDOSAGE

Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see ADVERSE REACTIONS). Symptoms were transient, and no serious clinical outcome has been reported when PRILOSEC was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.
As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.
Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

DOSAGE AND ADMINISTRATION

Short-Term Treatment of Active Duodenal Ulcer

The recommended adult oral dose of PRILOSEC is 20 mg once daily. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy (see INDICATIONS AND USAGE).

***H. pylori* Eradication for the Reduction of the Risk of Duodenal Ulcer Recurrence**

Triple Therapy (PRILOSEC/clarithromycin/amoxicillin) — The recommended adult oral regimen is PRILOSEC 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg each given twice daily for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of PRILOSEC 20 mg once daily is recommended for ulcer healing and symptom relief.
Dual Therapy (PRILOSEC/clarithromycin) — The recommended adult oral regimen is PRILOSEC 40 mg once daily plus clarithromycin 500 mg t.i.d. for 14 days. In patients with an ulcer present at the time of initiation of therapy, an additional 14 days of PRILOSEC 20 mg once daily is recommended for ulcer healing and symptom relief.
Please refer to clarithromycin full prescribing information for CONTRAINDICATIONS and WARNINGS, and for information regarding dosing in elderly and renally impaired patients (see PRECAUTIONS: General, PRECAUTIONS: Geriatric Use and PRECAUTIONS: Drug Interactions).
Please refer to amoxicillin full prescribing information for CONTRAINDICATIONS and WARNINGS.

Gastric Ulcer

The recommended adult oral dose is 40 mg once a day for 4–8 weeks (see CLINICAL PHARMACOLOGY, Clinical Studies, Gastric Ulcer, and INDICATIONS AND USAGE, Gastric Ulcer).

Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions is 20 mg daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20 mg daily for 4 to 8 weeks (see INDICATIONS AND USAGE).

Maintenance of Healing of Erosive Esophagitis

The recommended adult oral dose is 20 mg daily (see CLINICAL PHARMACOLOGY, Clinical Studies).

Pathological Hypersecretory Conditions

The dosage of PRILOSEC in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered. Daily dosages of greater than 80 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with PRILOSEC for more than 5 years.

Pediatric Patients

For the treatment of GERD or other acid-related disorders, the recommended dose for pediatric patients 2 years of age and older is as follows:

Patient Weight	Omeprazole Dose
< 20 kg	10 mg
≥ 20 kg	20 mg

On a per kg basis, the doses of omeprazole required to heal erosive esophagitis are greater than those for adults.
For pediatric patients unable to swallow an intact capsule, see Alternative Administration Options subsection below.

Alternative Administration Options

For patients who have difficulty swallowing capsules, the contents of a PRILOSEC Delayed-Release Capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.
No dosage adjustment is necessary for patients with renal impairment or for the elderly.
PRILOSEC Delayed-Release Capsules should be taken before eating. In the clinical trials, antacids were used concomitantly with PRILOSEC.
Patients should be cautioned that the PRILOSEC Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole.

HOW SUPPLIED

No. 3426 — PRILOSEC Delayed-Release Capsules, 10 mg, are opaque, hard gelatin, apricot and amethyst colored capsules, coded 606 on cap and PRILOSEC 10 on the body. They are supplied as follows:
NDC 0186-0606-31 unit of use bottles of 30
NDC 0186-0606-68 bottles of 100
NDC 0186-0606-28 unit dose packages of 100
NDC 0186-0606-82 bottles of 1000.
No. 3440 — PRILOSEC Delayed-Release Capsules, 20 mg, are opaque, hard gelatin, amethyst colored capsules, coded 742 on cap and PRILOSEC 20 on body. They are supplied as follows:
NDC 0186-0742-31 unit of use bottles of 30
NDC 0186-0742-28 unit dose package of 100
NDC 0186-0742-82 bottles of 1000.
No. 3428 — PRILOSEC Delayed-Release Capsules, 40 mg, are opaque, hard gelatin, apricot and amethyst colored capsules, coded 743 on cap and PRILOSEC 40 on the body. They are supplied as follows:
NDC 0186-0743-31 unit of use bottles of 30
NDC 0186-0743-68 bottles of 100
NDC 0186-0743-28 unit dose packages of 100
NDC 0186-0743-82 bottles of 1000.

Storage

Store PRILOSEC Delayed-Release Capsules in a tight container protected from light and moisture. Store between 15°C and 30°C (59°F and 86°F).

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2. NCCLS, Wayne, PA, January 2000.

Manufactured for: AstraZeneca LP, Wilmington, DE 19850
By: Merck & Co., Inc., Whitehouse Station, NJ 08889, USA

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Shown in Product Identification Guide, page 305

PULMICORT RESPULES®

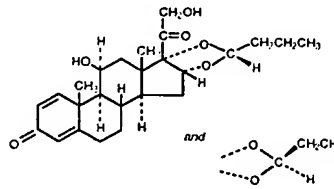
℞

[pŭl-mĭ-cŏrt]
(budesonide inhalation suspension)
0.25 mg and 0.5 mg
℞ only

For inhalation use via compressed air driven jet nebulizers only (not for use with ultrasonic devices). Not for injection. Read patient instructions before using.

DESCRIPTION

Budesonide, the active component of PULMICORT RESPULES®, is a corticosteroid designated chemically as (RS)-11β, 16α, 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6×10^3.
PULMICORT RESPULES is a sterile suspension for inhalation via jet nebulizer and contains the active ingredient budesonide (micronized), and the inactive ingredients disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80, and Water for Injection. Two dose strengths are available in single-dose ampules (Respules™ ampules): 0.25 mg and 0.5 mg per 2 mL RESPULE ampule.
For PULMICORT RESPULES, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance. Using the Pari-LC-Jet Plus Nebulizer/Pari Master compressor system, under *in vitro* conditions, the mean delivered dose at the mouthpiece (% nominal dose) was approximately 17% at a mean flow rate of 5.5 L/min. The mean nebulization time was 5 minutes or less.
PULMICORT RESPULES should be administered from jet nebulizers at adequate flow rates, via face masks or mouthpieces (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Mechanism of Action

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.
The precise mechanism of corticosteroid actions on inflammation in asthma is not well known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic- and non-allergic-mediated inflammation. The anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.
Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activities and systemic corticosteroid effects over a wide dose range of inhaled budesonide in a variety of formulations and delivery systems including Pulmicort Turbuhaler® (an inhalation-driven, multi-dose dry powder inhaler) and the inhalation suspension for nebulization. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85–95%) and the low potency of metabolites (see below).

Pharmacokinetics

The activity of PULMICORT RESPULES is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.
Budesonide is primarily cleared by the liver. In asthmatic children 4–6 years of age, the terminal half-life of budesonide after nebulization is 2.3 hours, and the systemic clearance is 0.5 L/min, which is approximately 50% greater than in healthy adults after adjustment for differences in weight.
After a single dose of 1 mg budesonide, a peak plasma concentration of 2.6 nmol/L was obtained approximately 20